Remarks

The specification has been amended to replace the Sequence Listing submitted on October 15, 2004, with the Sequence Listing submitted herewith. The replacement Sequence Listing indentifies the "Query" nucleotide sequence in Figure 1 as SEQ ID NO: 40.

In addition, the specification has been amended at the paragraph starting at page 4, line 35 to provide a sequence identifier and to further identify the described sequences as "Query" and "Sbjct", in accordance with Figure 1. Support for this amendment to the specification can be found in Figure 1.

Prior to this amendment, claims 5-21, 25-31, 33-41, 43-46, 49-59, and 61-73 were pending (of which claims 7, 14, 28-31, 33-41, 43-46, 49-59, and 61-64 are withdrawn). Claims 5, 6, 8-11, 15, 18, 19, 25, 27, 65, 68, 69, and 72 are amended herein and new claims 74-77 are added. Claim 7 is amended to depend from claim 18 and claim 72 is amended to depend from claim 15. Claims 9, 11, and 19 are amended to correct matters of form. Claim 61 is amended to incorporate the limitations of claim 62. Claims 16, 17, 54-58, 62, 66, 67, 70, 71, and 73 are canceled. Of the withdrawn claims, claims 7, 28, 45, 49, 59, 61, are amended to parallel the scope of the pending claims and claims 10, 14, 49, and 59 are amended to correct dependency.

Support for the amendment of claims 5 and 25 can be found at page 16, lines 17-21 and in Figure 5. Support for the amendment of claims 6-8, 25, 65 can be found in the specification at least at page 16, lines 7-16. Support for the amendment of claim 15, 27, 28, 45 can be found in the specification at page 14, lines 25-36. Support for the amendment of claim 18 can be found in the specification at least at page 9, lines 35-40. Support for the amendment of claims 68 and 69 can be found in the specification at least at page 2, lines 27-29. Support for new claim 74 can be found in the specification at least at page 2, lines 19-31. Support for new claim 75 can be found in the specification at least at page 9, lines 35 and 36 and page 10, line 39 through page 11, line 9. Support for new claims 76 and 77 can be found in the specification at least at page 16, lines 17-21 and in Figure 5.

No new matter is introduced by the foregoing amendments. After entry of this amendment, **claims 5-15, 18-21, 25-31, 33-41, 43-46, 49-53, 59, 61-65, 68-69, 72, and 74-77 are pending (of which claims 7, 14, 28-31, 33-41, 43-46, 49-53, 59, and 61-64 continue to be withdrawn).** Consideration and allowance of the pending claims are requested.

Examiner Interview

Applicants thank Examiner Nguyen for the courtesy of a telephone interview with their representative, Dr. Anne Carlson, on October 14, 2009. During the telephone interview the amendments of the claims were discussed. Although agreement was not reached on the final language of the claims, Applicants believe that the claims submitted herewith are in accordance with the telephone interview.

Withdrawal of Claim Rejections

Applicants thank Examiner Nguyen for withdrawing the rejection of claims 12-13 and 20-21 under 35 U.S.C. §101, the rejection of claims 15-17, 19-21, and 26-27 under 35 U.S.C. §102(e), and the rejection of claims 5, 15-18, and 26-27 under 35 U.S.C. §102(b) in the Final Office action dated April 24, 2009.

Sequence Non-Compliance

The specification is objected to for allegedly failing to comply with the requirements of 37 C.F.R. §§1.821-1.825 because the "application contains two different nucleotide sequences listed in Fig. 1 which were not identified with proper SEQ ID NOs in either the Fig. 1 or in the Brief Description of the Figures; nor were these nucleotide sequences listed in either a sequence paper listing or in a computer readable (CRF)" (Final Office at page 4). Applicants disagree, in part.

Applicants respectfully submit that the description of Figure 1 in the Brief Description of the Figures (see page 4, lines 35-36 of the specification) does, in fact, make reference to SEQ ID NO: 36 which is the lower (Sbjct) sequence in Figure 1. However, solely to advance prosecution in this case, the paragraph starting at page 4, line 35 is amended to recite that SEQ ID NO: 36 is

"residues 315187 to 314965 of human chromosome 12 genomic clone NT_009720 (Sbjct; SEQ ID NO: 36)." Support for this amendment of the specification can be found in original Figure 1.

The paragraph starting at page 4, line 35 also is amended to provide a sequence identifier (SEQ ID NO: 40) to the upper (Query) sequence in Figure 1. Finally, a substitute Sequence Listing is submitted herewith which includes SEQ ID NO: 40 (the "Query" sequence in Figure 1). Applicants submit that the above amendments fulfill the requirements of 37 C.F.R. §§1.821-1.825.

Objection to the Claims

Claims 25, 27, and 18 are objected to in the Final Office action dated April 24, 2009. Claim 25 is objected to because "the N-terminus of a polypeptide is usually referring to a single N-terminal amino acid residue" (Final Office action at page 4). Claim 25 is amended to replace N-terminus with "N-terminal sequence." Claim 5 is similarly amended to make this claim consistent with the language of amended claim 25. Support for the amendment of claims 5 and 25 can be found in the specification at least at page 27, line 39.

Claim 27 is objected to as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 27 is amended to recite that "the isolated nucleic acid molecule hybridizes under conditions of high stringency to the polynucleotide consisting of nucleotides 1-42 of SEQ ID NO: 37."

Claim 18 is objected to for depending from rejected claims 15 and 17. Claim 18 is amended herein to be in independent form. Applicants submit that this amendment of claim 18 renders this rejection moot with regard to elected species SEQ ID NO: 8. It is Applicants' understanding that claim 18 now contains allowable subject matter and the search should be extended to SEQ ID NOs: 6 and 10 under the terms of the election of species.

Applicants respectfully request that the objections to claims 18, 25 and 27 be withdrawn in light of these amendments.

Claim Rejections Under 35 U.S.C. §112, first paragraph (written description)

Claims 5-6, 8-13, 25, and 65-71 continue to be rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed (Final Office action dated April 24, 2009). Applicants respectfully traverse this rejection.

Claims 5 and 25 are amended to recite

". . . the polypeptide comprises:

a) an amino acid sequence at least 99% identical to SEQ ID NO: 8;

b) an amino acid sequence at least 95% identical to SEQ ID NO: 8, wherein fourteen consecutive amino acids within the N-terminal sequence of the polypeptide are identical to residues 1-14 of SEQ ID NO: 8; or

c) the amino acid sequence set forth as SEQ ID NO: 8,

wherein the polypeptide in a), b), or c) has RFX4_v3 activity"

Claims 6, 8-13, 65, 68, and 69 depend, directly or indirectly from claim 5, and incorporate all the limitations thereof. Claims 66, 67, 70 and 71 are canceled, rendering the rejection of these claims moot. The following remarks are based on the claims as currently amended.

The Office disputes Applicants' arguments and amendments submitted on April 24, 2008, alleging that "the claims encompass an isolated nucleic acid molecule encoding a RFX4_v3 polypeptide, wherein the polypeptide comprises any amino acid sequence at least 70% identical to any amino acid sequence set forth as SEQ ID NO: 8 (not necessarily limited to the full length amino acid sequence of SEQ ID NO: 8)" (Final Office action at page 10). As discussed above, Applicants have amended claims 5 and 25 to recite that "the polypeptide comprises a) an amino acid sequence at least 99% (or 95%) identical to SEQ ID NO: 8." Thus, Applicants respectfully submit that claims 5 and 25, as amended, are directed to a polypeptide having at least 99% (or 95%) sequence identity to the full length amino acid sequence of SEQ ID NO: 8.

The Office action also asserts that "there is no direct relationship between any particular sequence(s) with any of the RFX4_v3 activity" (Final Office action at page 11). Applicants disagree with the Office's assertion that an activity must be associated with a sequence in order to fulfill the written description requirement for a claimed genus under 35 U.S.C. §112. MPEP §2163 states that the "written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice . . ., reduction to drawings . . ., or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics" (emphasis added). As MPEP §2163 is written in the alternative, Applicants respectfully submit that there is no requirement that a structural or physical property be associated with a function in order to fulfill the written description requirement. Thus, the assertion that "there is no direct relationship between any particular sequence(s) with any of the RFX4_v3 activity" is irrelevant because the claimed genus is, in fact, defined by a structural or physical property (*i.e.* the amino acid sequence set forth as SEQ ID NO: 8), thereby fulfilling the written description requirement.

In addition, the Office disputes Applicants' argument that the N-terminal 14 amino acids of SEQ ID NO: 8 is an appropriate structural feature to define the claimed genus. Specifically, the Office alleges that Old *et al.* (U.S. 2003/0180298) discloses a "nucleic acid sequence for RFX4-E whose N-terminal region comprises identical 1-13 residues of SEQ ID NO: 8, and yet it is clearly a distinct molecule from RFX4_v3 or RFX4-D, and of course without any RFX4_v3 activity" (Final Office action at sentence bridging pages 7 and 8). Applicants disagree and note that the subject specification describes RFX4_v3 activity as "an activity that promotes the development of the brain's ventricular system, the *absence of which activity is demonstrated by the development of hydrocephalus*" (specification at page 11, lines 3-5, emphasis added). Thus, there must be a reduction in RFX4_v3 activity, compared to a control, to generate the phenotypic expression of congenital hydrocephalus. However, Old *et al.* does not attempt to reduce or knock out expression of RFX4-E. On the contrary, Old *et al.* teaches that astrocytomas have an over-expression of RFX4-E, compared to normal brain tissue (see Old *et al.*, paragraph [0350]).

As the development of hydrocephalus is a phenotype caused by under-expression of RFX4_v3, compared to a control, Applicants submit that without first correlating under-expression of RFX4-E with hydrocephalus, it is premature to conclude that RFX4-E does not have RFX4_v3 activity. Thus, without evidence to the contrary, Applicants submit that the N-terminal 14 amino acids of SEQ ID NO: 8 is, in fact, an appropriate structural characteristic in support of the claimed genus.

Applicants also disagree with the Office's allegation that in order to determine which RFX4_v3 polypeptide variants have activity, one must have knowledge of the "core structure(s) or element(s) that is responsible for the RFX4_v3 activity" (Final Office action at page 11). One of skill in the art need not be provided with a core structure in order to have possession of the genus of polypeptides has RFX4_v3 activity and (i) at least 99% identity to SEQ ID NO: 8 or (ii) at least 95% identity to SEQ ID NO: 8, wherein fourteen consecutive amino acids within the N-terminal sequence of the polypeptide are identical to residues 1-14 of SEQ ID NO: 8. In this instance, the specification clearly describes nucleic acid sequences encoding human (SEQ ID NO: 8) RFX4_v3 polypeptides (see, for example, the specification at page 16, lines at page 8, line 39; page 26, line 6 through page 31, line 36; and the sequence listing). In addition, the specification clearly describes nucleic acid sequences encoding RFX4_v3 polypeptide variants having 95% or 99% sequence identity with SEQ ID NO: 8 (see page 126, lines 7-11; page 29, lines 3-13; page 30, lines 24 -33). Moreover, conserved structural and functional domains (such as winged helix DNA-binding domain, dimerization domain, and B and C boxes; specification at page 1, lines 29-31; page 32, lines 6-9; and Figure 6), the amino terminal 14 amino acids (specification at page 25, lines 29-31), and conservative amino acid substitutions (see specification at page 16, lines 21-30; page 31, lines 3-23) were well known at the time the application was filed and provide additional guidance with regard to envisioning RFX4_v3 polypeptide variants. Finally, as various methods to detect expression of the RFX4_v3 polypeptide were well known and routine in the art at the time the application was filed, one of skill can test the variants to confirm that they have normal expression patterns (see Example 5 of the specification).

Thus, one of skill in the art, armed with the instant disclosure, information available in the art at the time the application was filed, and the provision of SEQ ID NO: 8 itself, would be able to envision the nucleic acid sequences encoding the polypeptides encompassed by the genus. Accordingly, the pending claims are sufficiently described by the specification, and Applicants request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Applicants note that splice variant RFX4_v4 has the closest sequence identity (98.3% sequence identity) to RFX4_v3 (SEQ ID NO: 8). Thus, a claim directed to an isolated nucleic acid molecule encoding a RFX4_v3 polypeptide, wherein the polypeptide comprises an amino acid sequence at least 99% identical to SEQ ID NO: 8 and has RFX4_v3 activity, does not read on splice variants of RFX4. Moreover, none of RFX4_v1, RFX4_v2, RFX4_v4, RFX4_v5, or RFX4_v6 splice variants have an amino acid sequence at least 95% identical to SEQ ID NO: 8, wherein fourteen consecutive amino acids within the N-terminal sequence of the polypeptide are identical to residues 1-14 of SEQ ID NO: 8. Thus, Applicants respectfully submit that the claimed isolated nucleic acid molecule encoding a RFX4_v3 polypeptide is not only sufficiently described by the specification, but is also novel.

Claim Rejections Under 35 U.S.C. §102

Claims 15-17, 19-21, 26-27, and 72-73 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Venter *et al.* (U.S. Patent No. 6,812,339) because Venter *et al.* discloses a nucleotide sequence (SEQ ID NO: 416) that is 72.3% identical to the nucleotide sequence set forth as SEQ ID NO: 37. Applicants respectfully traverse this rejection. Claims 16, 17, and 73 are canceled herein, rendering the rejection of these claims moot. Solely to advance prosecution in this case, claim 15 is amended to recite that the isolated nucleic acid molecule "hybridizes under conditions of high stringency to a polynucleotide consisting of nucleotides 1-42 of a nucleic acid sequence selected from the group consisting of SEQ ID NO: 37, SEQ ID NO: 38, and SEQ ID NO: 39, wherein the isolated nucleic acid molecule comprises at least 15 consecutive nucleotides of nucleotides 1-42 of SEQ ID NO: 37, SEQ ID NO: 38, or SEQ ID NO: 39, and wherein the isolated nucleic acid molecule encodes a RFX4_v3 polypeptide." As the Venter *et al.* sequence (SEQ ID NO: 416) aligns with only six consecutive residues of nucleotides 1-42 of SEQ ID NO: 37, the Venter *et al.* sequence does not comprise "at least 15

consecutive nucleotides of nucleotides 1-42" of SEQ ID NO: 37, SEQ ID NO: 38, or SEQ ID NO: 39, as required by amended claim 15. Thus, Venter *et al.* does not anticipate claim 15, as amended. Claims 19-21, 26, 27, and 72 depend, directly or indirectly, from claim 15 and incorporate all of the limitations thereof. Applicants respectfully request that the rejection of claims 15-17, 19-21, 26-27, and 72-73 be withdrawn in light of the current arguments and amendments.

Request for Rejoinder

The Examiner has required a restriction between product and process claims. The Applicants have elected claims to a specific product. In accordance with M.P.E.P. § 821.04, if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined. Applicants expressly request that the method claims be rejoined and the claims examined, at the latest upon the allowance of any of the product claims. It is believed that this is in accordance with the current Patent and Trademark Office Guidelines for Restriction Requirements in TC1600.

Conclusion

Based on the foregoing amendments and arguments, the claims are in condition for allowance and notification to this effect is requested. If any matters remain to be addressed before a Notice of Allowance is issued, the Examiner is formally requested to contact the undersigned prior to issuance of the next Office action, in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution.

Respectfully submitted,

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